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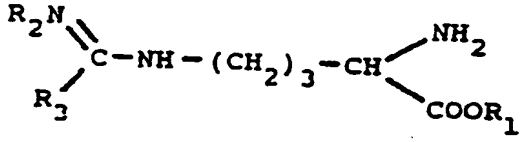
(58) Field of search
Online databases: CHABS, BIOSIS, MEDLINE

(54) Agents for blocking endothelin derived relaxing factor

(57) L-aminoacids of the formula



(R_1 = H, CH_3, C_2H_5; R_2 = H, NO_2; R_3 = NH_2, $NHCH_3$, NHC_2H_5, CH_3, C_2H_5) are useful for the treatment of shock states. Particular benefit is obtained by mixing the L-aminoacids with a cyclooxygenase blocker such as indomethacin or aspirin, and such compositions are claimed.

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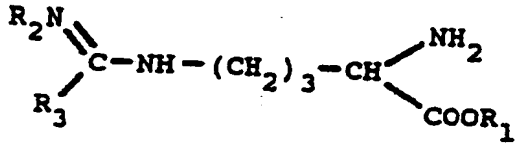
In particular, the blocking agents with which th invention is concerned are L-aminoacids of the general formula I



I

wherein R_1 represents a hydrogen atom or a methyl or ethyl group, R_2 represents a hydrogen atom or a nitr group and R_3 represents an amino, methylamino, ethylamino, methyl or ethyl group. These L-aminoacids are known compounds, having been disclosed in EP 230037 and other publications. However, their known use is as cytoprotective agents. We have found that these L-aminoacids are able to restore depressed response to catecholamines and to effectively inhibit vascular hyporeactivity.

Accordingly the invention provides use of an L-aminoacid as above defined for the preparation of a medicament for the treatment by perfusion of shock states.

The preferred L-aminoacids for this use are L-2-amino-5-(1-methylamino-1-imino-methylamino)-pentanoic acid (I : $R_1 = R_2 = H, R_3 = NHCH_3$) which is also known as L-N-monomethyl-arginine and is hereinafter referred to as "L-NMMA";

L-2-amino-5-(1-imino-ethylamino)-pentanoic acid (I : $R_1 = R_2 = H$, $R_3 = CH_3$) which is also known as L-iminoethyl--ornithine and is hereinafter referred to as "L-N10"; and

methyl L-2-amino-5-(1-nitroimino-1-amino-m thylamino)--pentanoate (I : $R_1 = CH_3$, $R_2 = NO_2$, $R_3 = NH_2$) which is also known as L-nitroarginine methyl est r and is hereinafter referred to as "L-NAME".

In some experiments, the endothelium was gently disrupted (-E). Phenylephrine (PE) induced contraction was stable over the time in control rings of animals receiving saline solution (0.9 % NaCl) with (E+) or without (E-) endothelium. The arginine derivative (10, 30 or 100 μM) had no significant effect per se.

Adversely, rings from animals treated with endotoxin showed, despite a similar contractile effect to PE, a loss of tonicity within the time referred as vascular hyporeactivity. This phenomenon was accentuated with intact endothelium (E+). The compounds of the invention (at 10, 30 or 100 μM) were able to reverse the loss of tonicity indicating that these compounds could inhibit the vascular hyporesponsiveness in preparations with or without endothelium.

The effect of the compounds of the invention was specific to the inhibition of EDRF generation whereas L-arginine, the natural precursor of nitric oxide, enhanced the loss of tonicity in endotoxin treated preparation.

In some experiments, the compounds of the invention were introduced in the bath 105 mn after PE when the tissue has completely its tonicity. In these conditions, the compounds of the invention, alone, were able to curatively and totally restore the contraction and therefore contribute extensively to vascular hyporesponsiveness to vasoconstrictor agents in shock. It has been also found that the action of the compounds of the invention might be strongly increased when associated to blockers of cyclooxygenase such as aspirin and indomethacin for instance. This was videnced by the following in vivo experimentation.

TOXICITY

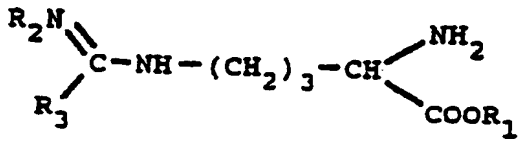
An acute toxicity study of the compounds of this invention has been conducted on rats and mice but no death was noticed at the maximum administrable dosis.

POSOLOGY

For the treatment of shock the usual posology comprises the administration by perfusion of 10 to 500 mg/hour, dissolved or suspended in a serum, of the select d compound of the invention, when used alone. The duration of treatment has to be determined in each case in relationship with a sufficient recovery of the patient. In case of co-administration of one of the compounds according to the invention with a blocker of cycloogenase, the dose for one hour of perfusion contains 10 to 100 mg of the selected compound according to the invention, associated with, 0.1 to 1 mg, if indomethacin is used, or 2 to 200 mg, if aspirin is used, or the corresponding amounts of other blockers of cycloogenase.

CLAIMS

1. Use of an L-aminoacid of the general formula



wherein R_1 represents a hydrogen atom or a methyl or ethyl group, R_2 represents a hydrogen atom or a nitro group and R_3 represents an amino, methylamino, ethylamino, methyl or ethyl group for the preparation of a medicament for the treatment by perfusion of shock states.

2. Use of L-2-amino-5-(1-methylamino)-1-imino-methylamino)--pentanoic acid for the preparation of a medicament for the treatment by perfusion of shock states.

3. Use of L-2-amino-5-(1-imino-ethylamino)-pentanoic acid for the preparation of a medicament for the treatment by perfusion of shock states.

4. Use of methyl L-2-amino-5-(1-nitroimino-1-amino--methylamino)-pentanoate for the preparation of a medicament for the treatment by perfusion of shock states.

5. A pharmaceutical composition comprising an L-aminoacid as defined in claim 1 in admixture with a cyclooxygenase blocker and with a pharmaceutically acceptable diluent or carrier.

6. A pharmaceutical composition comprising L-2-amino-5--(1-methylamino-1-imino-methylamino)-pentanoic acid) in admixture with a cyclooxygenase blocker and with a pharmaceutically acceptable diluent or carri r.